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Sex and Hormonal influences on Seizures and Epilepsy

Jana Velíšková[1,2] and **Kara A. DeSantis**[1,*]

[1]Department of Cell Biology & Anatomy, New York Medical College, Valhalla, New York, USA

[2]Department of Obstetrics & Gynecology, New York Medical College, Valhalla, New York, USA

Abstract

Epilepsy is the third most common chronic neurological disorder. Clinical and experimental evidence supports the role of sex and influence of sex hormones on seizures and epilepsy as well as alterations of the endocrine system and levels of sex hormones by epileptiform activity. Conversely, seizures are sensitive to changes in sex hormone levels, which in turn may affect the seizure-induced neuronal damage. The effects of reproductive hormones on neuronal excitability and seizure-induced damage are complex to contradictory and depend on different mechanisms, which have to be accounted for in data interpretation. Both estradiol and progesterone/allopregnanolone may have beneficial effects for patients with epilepsy. Individualized hormonal therapy should be considered as adjunctive treatment in patients with epilepsy to improve seizure control as well as quality of life.

Keywords

epilepsy; neuronal excitability; seizure-induced damage; estradiol; progesterone; allopreganalone; sex differences; anticonvulsant drugs

Epilepsy is the third most common chronic neurological disorder accounting for about 1% of disease-affected population worldwide. Epilepsy is characterized by occurrence of unprovoked seizures accompanied by complex symptoms arising from broad disorder of brain function. Despite extensive research on epilepsy and seizure mechanisms, treatment is still limited to symptomatic rather than mechanism-oriented approaches. Most importantly, about one third of patients with epilepsy have intractable seizures, which do not respond to treatment with current anticonvulsant drugs. Since epilepsy is not a single syndrome but rather comprises variety of pathological processes with extensive dysfunction of the brain, antiepileptic treatment should not be limited only to anticonvulsant therapy but the patients may also benefit by adjunctive strategies (Vezzani et al., 2011).

Population-based epidemiological studies suggest that prevalence and incidence of seizures and epilepsy is slightly higher in males than in females (Hauser et al., 1991; McHugh and Delanty, 2008). Despite the fact that the sex differences in the incidence of epilepsy do not reach a significant difference, consistent trend reported across studies suggests that males have higher risk than females for seizures and epilepsy.

In addition to sex differences in seizure expression, reproductive/sex hormones can also influence seizure susceptibility. Besides their main role on the tissue of reproductive organs,

Correspondence: Jana Velíšková, MD, PhD, New York Medical College, Department of Cell Biology & Anatomy, Basic Medical Sciences Bldg., Room #A21, Valhalla, NY 10595, USA, jana_veliskova@nymc.edu, Phone: (914) 594-4840, Fax: (914) 594-4653.
*Current affiliation: Graduate Program in Molecular, Cellular, Developmental, and Neural Biology, Department of Biological Sciences, University at Albany, State University of New York, Albany, NY, USA

sex hormones are critical for normal brain functions through affecting and regulating neuronal excitability and survival. Thus not surprisingly, clinical and experimental studies show that seizures reflect changes in sex hormone levels; in some women with epilepsy, seizure exacerbation can be related to periodical hormonal fluctuations during the ovarian cycles, a condition called catamenial epilepsy (Herzog et al., 1997; Reddy and Rogawski, 2009). Seizures also often change pattern, expression or onset at the time of natural hormonal changes such as adolescence (Klein et al., 2003; Wheless and Kim, 2002), pregnancy (Tomson and Battino, 2009a), and during the perimenopause and menopause (Harden et al., 1999).

This review will highlight some clinical and experimental evidence in support to the role of sex and influence of sex hormones on seizures and epilepsy. A plethora of reviews have been written on the presumed excitatory effects of estrogens and inhibitory effects of progesterone (Morrell, 1992; Reddy, 2009; Scharfman and MacLusky, 2006; Woolley, 1999). However, we will argue here that the effects of sex hormones on neuronal excitability, seizures, and seizure-induced damage involve complex mechanisms difficult to separate as they range from regulation of gene expression to rapid effects via activation of various membrane receptors including specific hormone receptors, orphan G-protein coupled receptors, or acting as promiscuous ligands on neurotrophin and ion-channel coupled receptors [also reviewed previously (Velíšková, 2006b; Velíšková, 2007)]. In particular in this review we will specifically highlight the controversial data, which are often overlooked and not discussed in most studies and reviews.

Role of sex in epilepsy and sex-specific effects of sex steroid hormones on seizure susceptibility

During childhood, seizures and epilepsy syndromes more likely affect boys than girls, although some epilepsies are significantly more common or exclusive in girls than in boys (for sex differences in incidence of some epilepsy syndromes see Table 1). Sex related differences have been described also in patients with temporal lobe epilepsy, with respect to distinct regional distribution of brain dysfunction during interictal periods, seizure generalization, lateralization, as well as the extent of neuronal damage (Janszky et al., 2004; Savic and Engel, 1998).

Animal data confirm clinical observations and the studies report sex differences in susceptibility using different seizure models. However, available data are insufficient to draw clear conclusions on possible mechanisms as demonstrated on following examples: In a model of primarily generalized seizures induced by intraperitoneal administration of $GABA_A$ receptor antagonist picrotoxin, female rats were more sensitive compared to male rats (Pericic and Bujas, 1997b; Pericic et al., 1986; Pericic et al., 1985; Thomas, 1990). One would assume that such finding in rats confirms the clinical data showing that primary generalized seizures are more common in women than in men (Christensen et al., 2005). However, the following evidence documents that conclusions drawn from animal data requires to take into consideration many variables among the studies and thus, warrants cautious interpretation: (1) Sensitivity to picrotoxin-induced seizures seems to depend on dose of the convusant: Female rats were more sensitive to picrotoxin-induced clonic and tonic-clonic seizures than males only when a low dose of picrotoxin has been used. High doses of picrotoxin had a different effect; males developed clonic seizures faster compared to females and no sex differences have been found in the onset of tonic-clonic seizures (Thomas, 1990). (2) Injection of another $GABA_A$ receptor antagonist bicuculline did not show any sex differences in seizure susceptibility but when the rats were exposed to stress prior to seizure testing, males developed bicuculline-induced seizures faster than females (Pericic and Bujas, 1997a; Pericic and Bujas, 1997b). Thus, investigation of two models of

primarily generalized seizures with similar mechanism of action leads to different findings though one may argue that the main outcome of the stress/bicuculline experiment is that females handle stress better than males. (3) Route of administration of the convulsant drug represents another important variable. Unlike the intraperitoneal administration (used in studies described above), males were more susceptible to seizures compared to female rats after intravenous injection of both picrotoxin or bicuculline (Pericic and Bujas, 1997b). (4) Interspecies differences also need to be considered. Findings in mice are quite opposite to rats. Female mice were more resistant to picrotoxin-induced seizures compared to male mice following intraperitoneal administration (Pericic and Bujas, 1997b; Pericic et al., 1986). While male mice were more sensitive to intravenous injection of bicuculline compared to female mice, both sexes were equally sensitive to intravenous picrotoxin-induced seizures (Pericic and Bujas, 1997b). There is no clear explanation for the above-mentioned differences but possible mechanisms may include interspecies differences in GABA binding, sex differences in GABA content, or differences in the convulsant drug metabolism following intraperitoneal or intravenous injection (Pericic and Bujas, 1997b). It should be also noted here that in these studies females were tested for seizure susceptibility randomly irrespective to the cycle stage. Although, there is paucity of studies testing the effects of estrous cycle in females on seizures, individual stages may not play a significant role in seizure susceptibility. A study using pilocarpine-induced seizures showed no effect of estrous cycle on clonic seizure onset (Scharfman et al., 2005).

In models of temporal lobe seizures induced by either kainic acid or pilocarpine, secondary generalized clonic seizure in males were more severe and more frequent compared to female rats and this effect has been linked to testosterone levels (Mejias-Aponte et al., 2002). This is an interesting finding raising a question of underlying mechanisms of the proconvulsant effects of testosterone (Frye, 2006; Frye, 2010). The likely mechanism seems to involve aromatization of testosterone to estradiol, which mediates excitatory effects in males in contrast to females as suggested by data from both clinical and animal studies: First, a clinical trial in male patients with temporal lobe epilepsy showed that administration of aromatase inhibitors such as anastrazole or letrozole, which block the conversion of testosterone to estradiol, results in reduction of seizures (Harden and MacLusky, 2005; Herzog, 1999). Aromatase inhibition can provide an additional beneficial effect and that is an increase in testosterone levels, which are generally low in men with temporal lobe epilepsy probably due to enhanced aromatization of testosterone (Harden and MacLusky, 2005). Second, daily repeated administration of β-estradiol had proconvulsant effects on pilocarpine-induced seizures and enhanced severity of kainic acid-induced seizures in male but not in ovariectomized female rats (Galanopoulou et al., 2003; Nicoletti et al., 1985). These data are in accordance to sex-specific sensitivity of the hippocampus, one of the leading structures involved in temporal lobe seizures, to sex hormones. *In vitro* recordings showed that in slices from male rats, bath application of testosterone itself had no effect on population spike amplitude in the CA1 region but bath application of β-estradiol to slices from males dramatically increased the population spike amplitude (Teyler et al., 1980). In contrast, in slices from female rats regardless of the estrous cycle stage, bath application of β-estradiol had no effect on the CA1 population spike amplitude (Teyler et al., 1980). On the other hand, bath application of testosterone to slices from female rats had biphasic effects depending on the estrous cycle stage. In slices from females in diestrus, testosterone had transient excitatory effects but it inhibited synaptic activity in slices from proestrus females (Teyler et al., 1980). Thus, these data clearly demonstrate that hippocampal tissue from males is more sensitive to estradiol but not testosterone itself compared to females. On the other hand, in female hippocampus, estradiol did not enhance neuronal excitability.

Effects of progesterone against kainic acid-induced seizures are also sex-specific: in females, progesterone has anticonvulsant effects while in males the effect is proconvulsant (Nicoletti et al., 1985).

Taken together, sex differences and distinct effects of sex hormones on neuronal excitability and seizure susceptibility or expression can be influenced by many factors including the presence of sexual dimorphism in brain regions responsible for generation and control of seizures, in regional connectivity, in neurotransmitter systems, and in receptor distribution, binding, and sensitivity (McCarthy and Arnold, 2011; Taylor, 1969; Velíšková, 2007; Velíšková and Moshe, 2006).

Effects of female sex hormones on seizures and neuronal excitability in females

The importance of sex hormone action in the brain is underscored by reports showing that neurons and glia are equipped for local *de novo* production of steroid hormones in the central nervous system (CNS) (Lavaque et al., 2006), including the human hippocampus (Stoffel-Wagner et al., 2000). By a strict definition, only these locally produced hormones from cholesterol should be called “neurosteroids” (Majewska, 1992). A more widely use of the term includes also the steroid hormone metabolites locally converted in the CNS from the peripheral source of gonadal hormones, as steroid hormones easily cross the blood-brain barrier due to their lipophilic properties and small molecular size. During reproductive age, the gonads are the main source of hormones for the *in situ* conversion to neurosteroids in the CNS. The local steroid hormone synthesis in the CNS is low. Once the peripheral source of steroid hormones is insufficient (such as at menopause) *de novo* synthesis of a steroid hormone increases (Veiga et al., 2004). Regarding hormonal levels within the brain tissue as a function of estrous cycle phases, studies report (1) striking inter-regional differences in estradiol and progesterone or its metabolites (e.g., up to 5 fold higher levels in cortex than in hippocampus), as well as (2) changes in estradiol and progesterone metabolite (allopregnanollone) but not progesterone itself as a function of estrous cycle stage (Koonce et al., 2012). However, involvement of individual hormone changes in seizure modulation would require determining their levels preferentially within structures responsible for seizure initiation (i.e., amygdala, hippocampus, area tempesta…) and control/termination (i.e., substantia nigra, striatum, superior colliculus…) to draw any correlation between their levels and seizure onset. Levels of individual hormones within the brain tissue differ depending on brain region, for example, hippocampal tissue levels of estradiol are low compared to circulating estradiol levels; gonadectomy reduces estradiol levels while exogenous hormonal replacement enhances the levels in the hippocampus above those found in intact animals (Barker and Galea, 2009; Konkle and McCarthy, 2011).

Neurosteroids are known for their non-genomic acute effects by direct modulation of NMDA receptors and $GABA_A$ receptors. Neurosteroids are responsible mainly for “fine tuning” of neuronal excitability by acting at synaptic and extrasynaptic receptors (Lambert et al., 2009). Besides that, neurosteroids also play an important role in neuronal survival in developing as well as aging brain and disturbances in the neurosteroid production have been detected in sclerotic hippocampal tissue from patients with temporal lobe epilepsy (Yague et al., 2010) and other neurodegenerative disorders (such as Alzheimer disease or multiple sclerosis), which are associated with increased incidence of seizure disorders (Larner, 2010; Luchetti et al., 2011; Vincent and Crino, 2011).

Surges in peripheral sex hormone during distinct maturation periods also affect brain function and seizure outcomes, e.g., by inducing sexual differentiation of regions responsible for seizure control or initiation, or brain maturation (Velíšková, 2009; Velíšková

and Moshe, 2006). Some epileptic syndromes may either remit (benign rolandic epilepsy, childhood absence) or have their onset (juvenile myoclonic epilepsy) in adolescence, indicating the likely influence of hormonal changes and maturation occurring around puberty (Cramer et al., 2007; Klein et al., 2003).

During pregnancy, some women may report decrease in seizure frequency, others report worsening of seizure control (Schmidt, 1982). However, seizure worsening during pregnancy may not be only related to hormonal changes but also to the fact that some women may stop their anticonvulsant treatment because of worries of birth defects (Morrell, 1995). Although some anticonvulsant drugs are associated with birth defects, seizure control during pregnancy is an important goal (Pennell, 2004; Tomson and Battino, 2009b). This issue has been well recognized and principles and guidelines for seizure control with special attention to minimize the risk for the mother and the fetus have been described in several excellent reviews (Burakgazi et al., 2011; Morrell, 2001; Tomson and Battino, 2009a; Tomson and Battino, 2011).

In some women, changes in seizure frequency have been observed in association with menstrual cycles, a condition called catamenial epilepsy (Backstrom, 1976; Bandler et al., 1957; Herzog et al., 1997; Laidlaw, 1956). A detailed review on catamenial epilepsy is part of this issue and thus we will highlight only some controversial aspects. Several mechanisms responsible for a catamenial pattern of seizures in epileptic women have been proposed. These mechanisms include but are not limited to changes in estrogen/progesterone ratio, progesterone withdrawal, changes in water content, fluctuations in calcium levels, interactions of anticonvulsant drugs and steroid hormones, thyroid hormone deficiency (Backstrom, 1976; Bandler et al., 1957; Bauer, 2001a; Bauer, 2001b; Gordon, 1909; Herzog et al., 1997; Moran and Smith, 1998; Newmark and Penry, 1980), or many other factors, which have not been addressed by previous studies, e.g., increased testosterone levels or LH levels (both hormones increased in women with epilepsy due to anovulatory cycles, polycystic ovaries, or seizures themselves) (Herzog et al., 1984; Herzog et al., 1986b). Some authors linked the increase in frequency of partial as well as secondary generalized seizures to high estrogen/progesterone ratio (Backstrom, 1976; Herzog et al., 1997). However, the high estrogen/progesterone ratio could not consistently explain seizure exacerbation in all presented cases (Backstrom, 1976). In contrast, another study reported that in women with primary generalized epilepsy, fewer seizures occurred when estrogen levels were high at the mid-cycle and more seizures occurred when estrogen levels were low, during both follicular and luteal stage (Jacono and Robertson, 1987).

Periodic changes in seizure frequency with a cycle between 8–46 days have been also reported in men or prepubertal girls. Interestingly in some, seizures may also reappear with periodicity of 28 days similar to women at reproductive age [for review see (Newmark and Penry, 1980)]. The reason for triggers of such periodic seizure exacerbation in men and prepubertal girls is, however, unknown (personal communication with Dr. Quigg).

Animal studies show decrease in spontaneous seizures during pregnancy and lactation using pilocarpine or kainic acid models of temporal lobe epilepsy (Amado and Cavalheiro, 1998; Berzaghi Mda et al., 1987). Most importantly, many studies stress the critical role of maternal seizure control during pregnancy to prevent serious behavioral consequences in offspring (do Vale et al., 2010; Lima et al., 2010; Novaes et al., 2012; Raffo et al., 2009).

There are only a few animal studies, which tested severity of seizures depending on individual phases of estrous cycles in female rats. A study by Frye and Bayon (Frye and Bayon, 1999) showed that rats in proestrus/estrus spent less time in kainic acid-induced seizures compared to rats in metestrus/diestrus. The authors focused on allopregnanolone

(progesterone metabolite acting as $GABA_A$ receptor agonist) levels and found negative correlation between allopregnanolone levels and seizure duration. Thus the authors concluded that allopregnanolone withdrawal is associated with prolonged seizure duration, while high levels of allopregnanolone correlate with shorter seizure duration (Frye and Bayon, 1999). Another study used pilocarpine seizure model and found that rats in estrus are less prone to develop status epilepticus compared to rats in other phases of estrous cycle (Scharfman et al., 2005), an effect that possibly could be also related to allopregnanolone protective effects based on the findings of the previously mentioned study showing that allopregnanolone levels are elevated during estrus (Frye and Bayon, 1999).

Animal studies using ovariectomized rats with hormonal replacement show that sex hormones influence neuronal activity either through excitatory or inhibitory mechanisms. However, data in the literature brings controversial findings on the effects of sex hormones on neuronal excitability and seizures likely because of complexity of sex hormone action, which also depends on many factors including the type of hormone, on species of a hormone (natural or synthetic), sex, age, regional distribution of hormone receptors, treatment duration, time interval for initiation of hormonal treatment following gonadal removal (if any), route of administration, as well as the dose. The various mechanisms involved in these controversies have been reviewed in detail previously (Velíšková, 2006b; Velíšková, 2007). Thus, here we will highlight just a few examples. Hormone dose used in the studies represents one of the important reasons for controversial findings among the outcome from different laboratories. Estrogens are more potent compared to progesterone (for physiological range of ovarian hormones in women during ovarian cycle see Table 2); circulating estrogen levels are thousand times lower compared to circulating physiological levels of progesterone. Thus, the doses of estradiol chosen in many studies are often supraphysiological, while animals treated with progesterone are less often overdosed (Table 2). Supraphysiological doses of either hormone likely result in different effects compared to doses within physiological range (Velíšková, 2006b; Velíšková, 2007). A study by Hoffmann et al., 2003 (Hoffman et al., 2003) compared effects of different doses of progesterone replacement in female rats after ovariectomy on kainic acid-induced seizures and showed that lower doses of progesterone (within physiological range) were associated with decreased severity of kainic acid-induced seizures compared to rats without hormonal replacement; i.e., progesterone had anticonvulsant effects. However, in female rats treated with supraphysiological doses of progesterone, there was no difference in seizure severity compared to ovariectomized controls, thus at high doses progesterone lost its anticonvulsant properties (Hoffman et al., 2003). The most intriguing finding in this study was the positive correlation between progesterone serum levels and seizure severity, animals with high progesterone serum concentration (reaching supraphysiological levels) experienced significantly more severe seizures than animals with progesterone concentrations within physiological levels (Hoffman et al., 2003). The authors did not find any difference in seizure severity in estradiol-treated animals using doses around 24 μg/day and 5 μg/day (see Table 2) compared to ovariectomized controls (Hoffman et al., 2003). The study did not report effects of progesterone or estradiol on the onset of kainic acid-induced seizures (seizure threshold), which is another measure used in studies comparing proconvulsant versus anticonvulsant effects of a treatment. Such data are available from studies by others (for estradiol serum concentrations following individual treatment paradigms see Table 2): Estradiol administration in a dose of 2 μg/day injected for several days (2 or 4) significantly delayed the kainic acid-induced clonic seizure onset, thus had an anticonvulsant effect compared to oil-injected ovariectomized controls (Velíšková and Velíšek, 2007; Velíšková et al., 2000). Administration of 10 μg/day of estradiol for 2 days accelerated the onset of kainic acid-induced clonic seizures, thus estradiol had a proconvulsant effect (Woolley, 2000) but a follow up study did not find accelerated onset of clonic seizures following a single 10 μg/day estradiol injection (Ledoux et al., 2009). Interestingly, another study

reported that only administration of 40 μg/day of estradiol accelerated kainic acid-induced seizures but 20 μg of estradiol for 1 or 7 days had no effect on clonic seizure onset confirmed by EEG recordings (Reibel et al., 2000). These data are similar to findings of Hoffman et al. (Hoffman et al., 2003). In addition, *in vitro* bath application of either estradiol or progesterone facilitated synaptic transmission in neocortical slices from female rats in a dose-dependent manner: Low doses of either hormone had no effect while high doses enhanced the amplitude of spreading depression (Sachs et al., 2007). Finally, administration of estradiol for 4 or 10 days in a dose of 2 μg/day to naive females inducing thus supraphysiological levels of estradiol accelerated kainic acid-induced clonic seizure onset (Nicoletti et al., 1985; Velíšková, 2007). However, it should be noted here that in non-ovariectomized animals progesterone might interfere with estradiol effects. Several studies showed that progesterone addition often reverses estradiol effects (Velíšek et al., 1999; Weiland, 1992; Woolley and McEwen, 1993).

Underlying mechanisms for the various findings in sex hormone effects on seizures are still unknown. The most important difference seems to be the physiological versus supraphysiological doses of estradiol or progesterone used among the studies as discussed above. However, we can speculate that other differences in treatment paradigms can also explain at least some discrepancies among the studies. The interval between ovariectomy and seizure testing (4 versus 11 or more days) is an important factor. For example, ovariectomy leads to decrease of glutamic acid decarboxylase (GAD), the rate-limiting enzyme for GABA synthesis (Nakamura et al., 2004; Nakamura et al., 2005; Weiland, 1992). However, the GAD levels decrease for over several days and the low levels are not established up to 10 days following ovariectomy (Nakamura et al., 2005). Differences may also be due to hormone replacement duration [a single dose versus replacement for several days (Velíšková et al., 2010; Velíšková and Velíšek, 2007)]. Finally, one cannot ignore differences in other non-hormonal factors such as light rhythms (lights on during the day or reversed dark/light cycles), housing of animals (individual versus in groups), type of anesthesia used during ovariectomy (methoxyflurane versus ketamine, especially when seizure testing follows a short-term postovariectomy period), or the dose of the convulsant agent (Velíšková, 2006a).

Thus, the above-presented data from animal studies clearly illustrate that both progesterone and estradiol in doses not exceeding the physiological levels have seizure limiting properties. Both hormones can delay the onset of seizures and prevent mortality, however progesterone administration has more powerful anticonvulsant properties and more consistent effects on decreasing severity of seizures compared to estradiol (Hoffman et al., 2003; Ledoux et al., 2009; Reibel et al., 2000; Velíšková and Velíšek, 2007; Velíšková et al., 2000). Possible mechanisms involved in the antiseizure effects of estradiol may include enhancement of expression and release of NPY, estradiol-stimulated formation of allopregnanolone in the hippocampus, or enhanced expression of GAD (Ledoux et al., 2009; Nakamura and McEwen, 2005; Nakamura et al., 2005; Osborne and Frye, 2009; Velíšková and Velíšek, 2007; Weiland, 1992). Progesterone-induced anticonvulsant effects seem to be mediated via its metabolite allopregnanolone, which activates $GABA_A$ receptors (Frye et al., 2002; Reddy, 2010). In contrast, doses of both sex hormones resulting in supraphysiological concentrations may enhance seizure susceptibility and these effects may be due to enhanced NMDA-mediated transmission due to increased dendritic spine density by either estradiol or progesterone (Morali et al., 2012; Woolley and McEwen, 1993).

In conclusion (see Table 3), we would like to emphasize that there is not a single study showing proconvulsant effects of chronic estradiol replacement in ovariectomized rats (tested more than one week following ovariectomy) using estradiol doses up to 20 μg/day in the kainic acid-induced seizure model (Hoffman et al., 2003; Reibel et al., 2000; Velíšková

and Velíšek, 2007; Velíšková et al., 2000). There is an exception in a study by Šlamberová and Vathy (Šlamberová and Vathy, 2000), which reported a proconvulsant effect of estradiol in a dose of 3 μg/day on kainic acid-induced seizures. As mentioned above, the shortcomings of this study are that the animals were prenatally exposed to stress because of saline injections to dams for one week (Šlamberová et al., 2002), further these animals were maintained on reversed dark/light cycles, and housed individually after weaning. Post-weaning social isolation induces serious consequences in rats including increased sensitivity to anxiety and stress-related responses (Lukkes et al., 2012; Thielen et al., 1993; Weintraub et al., 2010). As seizures are associated with rapid release of stress hormones (Frye and Walf, 2011), the study cannot be used as an example of seizure-modulating effects of estradiol.

Loss of gonadal hormones and seizures

A natural menopause is a permanent cessation of ovarian function and occurs in control women without epilepsy between ages 45 and 55. Women with epilepsy have increased risk for premature onset of menopause (Harden et al., 2003). Depending on seizure frequency and estimated lifetime number of seizures, the ovarian failure in women with epilepsy occurs as early as around age 40 (Klein et al., 2001). The dramatic irregular fluctuations in gonadal hormones during the onset of menopause (perimenopausal stage) and their loss at menopause are likely to influence seizure frequency. However, the studies report controversial findings. A study by Harden et al., 1999 showed that women with non-catamenial pattern of seizures during their reproductive age reported worsening of seizure control or no change at menopause, while women with catamenial pattern of epilepsy reported better control of their seizures when reaching the menopause (Harden et al., 1999). Similarly, another study describes that about 40% of women with epilepsy reported worsening of their seizures after the menopause, some women had new onset of seizures, while only 18% reported better seizure control after the menopause (Abbasi et al., 1999).

The decline in estradiol levels following cessation of ovarian function is associated with increased risk for cardiovascular disease, osteoporosis, or vasomotor symptoms. Hormone replacement therapy (HRT) to relieve the hot flashes or prevent osteoporosis is, however, prescribed much less commonly in women with epilepsy than in general population. This is despite the fact that especially women with epilepsy treated with enzyme-inducing anticonvulsant drugs such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, topiramate or sodium valproate, which decrease the levels of vitamin D, are at higher risk of osteoporosis and osteomalacia (Pack, 2011). Data on effects of HRT on seizure frequency in women with epilepsy are controversial. Current studies, however, clearly support the idea that the estrogen species used in the HRT is important. Several studies have shown that equine conjugated estrogens (which do not include β-estradiol, the main estrogen species in humans) usually exacerbate the seizures (Harden et al., 2006), while the HRT initiated as β-estradiol monotherapy in a menopausal woman was associated with improved seizure control (Peebles et al., 2000).

Several studies have shown that addition of sex hormones interferes with levels of some anticonvulsant drugs and vice versa. Thus, special considerations for HRT strategy adjustments are critical in women with epilepsy for full benefits of HRT without the risk of seizure exacerbation (Harden, 2008).

Animal studies are mostly done on young adult ovariectomized animals. Ovariectomized rats are more susceptible to seizures. In the pilocarpine model of temporal lobe seizures, ovariectomized females demonstrated significantly faster progression to status epilepticus and faster progression from a first sign of abnormal behavior to clonic seizures compared to

naive cycling females (Scharfman et al., 2005). Several other studies have shown that ovariectomized rats had earlier seizure onset compared to females with β-estradiol replacement (Kalkbrenner and Standley, 2003; Schwartz-Giblin et al., 1989; Tominaga et al., 2001; Velíšková et al., 2010; Velíšková and Velíšek, 2007; Velíšková et al., 2000). Finally, ovariectomized animals have high mortality rate following status epilepticus compared to naive rats and compared to animals with estradiol or progesterone replacement (Hoffman et al., 2003; Ledoux et al., 2009; Scharfman et al., 2005; Velíšková et al., 2000; Woolley, 2000).

It is important to emphasize that the final outcome also depends on the interval between ovariectomy and seizure testing or initiation of hormonal replacement (Bohacek et al., 2008; Bohacek and Daniel, 2009; Miranda et al., 1999; Nakamura et al., 2004; Nakamura et al., 2005).

Mechanism-based differences between effects of estradiol and progesterone

Sex hormones exert their action on neurons either by changes in gene expression (up- or down-regulation), by modulating membrane excitability through their own membrane receptors, at orphan G protein-coupled receptor, GPR30, but also acting as promiscuous ligands at neurotrophin, neurotransmitter receptors, or ion channels (Foy et al., 2010; Jensen et al., 2010; McEwen, 2002; Spencer et al., 2008; Toran-Allerand, 2004; Woolley, 2007). Classical genomic effects of sex hormones are mediated by activation of intracellular receptors, which are specific for individual hormones and can be found either in the cytoplasm or within the nucleus. Binding of a hormone to intracellular receptors mediates regulation of gene expression at the nuclear level. The subsequent effects have delayed onset but long duration, which extends beyond the period of the hormone presence in the tissue (McEwen, 2002). In contrast, non-genomic effects involve rapid changes in neuronal excitability by activation of membrane-bound receptors as well as directly regulating neurotransmitter receptors or ion channels. Direct membrane effects of steroid hormones last only during the period when the hormone is present for binding to the receptor (McEwen, 2002; Woolley, 2007).

The controversial findings on estradiol and progesterone effects on seizure susceptibility seem to involve still underappreciated complexity of action of steroid hormones. Pathologic mechanisms of seizure disorders seem to be responsive to both genomic and non-genomic effects of estradiol and rather to acute non-genomic effects of progesterone. Interestingly, a recent study using progesterone receptor knockout mice stresses an important role of signaling pathways mediated by progesterone receptors in epileptogenesis (Reddy and Mohan, 2011) and warrants more studies in these directions. The dose of individual hormone used in the studies is an important determinant for its final effect. In addition, progesterone mainly acts via its metabolites, while estradiol rather acts directly to mediate its genomic and non-genomic effects.

Chronic administration of progesterone has the same anticonvulsant effect as acute pretreatment just before seizure testing, but only doses producing serum levels within physiological range are effective (Frye et al., 2002; Hoffman et al., 2003; Reddy and Rogawski, 2001). These anti-seizure effects of progesterone are accredited to its metabolite allopregnanolone (3α-OH-5α-pregnan-20-one) (Frye et al., 2000; Frye et al., 2002; Herzog and Frye, 2003; Lonsdale et al., 2006). Effects of allopregnanolone are acute, non-genomic, and robust as expected from a positive allosteric modulator of $GABA_A$ receptors (Lambert et al., 2009). However, similarly as other allosteric modulators of $GABA_A$ receptors such as benzodiazepines or barbiturates, use of allopregnanolone as long-term anticonvulsant

therapy may be limited because of development of tolerance (Turkmen et al., 2011). In addition, chronic administration of allopregnanolone contributes to a paradoxical hyperexcitability state by increasing the expression of α4subunit of $GABA_A$ receptors (denotes the extrasynaptic receptors insensitive to benzodiazepines) (Smith et al., 2007). The hyperexcitability could be also related to progesterone-induced increase in dendritic spine density with mushroom like spines (Morali et al., 2012), which is similar to estradiol effects (Woolley and McEwen, 1994) and to positive modulation of NMDA receptors and glutamate release (Giuliani et al., 2011). Finally, epileptiform activity causes changes in $GABA_A$ receptor subunit composition, which then in turn leads to decreased sensitivity of the $GABA_A$ receptors to ligands, including neurosteroids (Joshi et al., 2011).

Estradiol has mixed effects when administered acutely ranging from no effect, mild anticonvulsant to proconvulsant effects on seizures mainly depending whether physiological or supraphysiological doses have been used (Gevorkyan et al., 1989; Nicoletti et al., 1985; Velíšková et al., 2010). Nevertheless as mentioned above, besides the fact whether reports on estradiol effects show proconvulsant or anticonvulsant effects, studies generally agree that estradiol pretreatment significantly decreases status epilepticus-related mortality and severity of seizures (Ledoux et al., 2009; Scharfman et al., 2005; Velíšková et al., 2000; Woolley, 2000). Seizure limiting effects of estradiol have been linked mainly to regulation of neuropeptide Y (NPY) in the hippocampus (Ledoux et al., 2009; Nakamura and McEwen, 2005; Velíšková and Velíšek, 2007). NPY is a powerful inhibitory peptide modulating neuronal excitability by mechanisms such as regulation of glutamate release, intracellular Ca^{2+}, or voltage gated Ca^{2+} channels (Sperk et al., 2007). A single injection as well as repeated daily administration of estradiol facilitates NPY release and repeated administrations of estradiol over several days also enhance NPY expression within the hippocampus (Ledoux et al., 2009; Nakamura and McEwen, 2005; Velíšková and Velíšek, 2007).

Effects of sex and female gonadal steroid hormones on seizure-induced neuronal damage

Epilepsy can be associated with neuronal damage. Temporal lobe epilepsy is a well-known epileptic syndrome associated with such neuronal injury, especially within the limbic structures but also with atrophy in other regions namely the cortex (Engel Jr. et al., 1997; Mathern et al., 1996). Little is known from clinical studies about the relationship between sex and sex steroid hormone levels on seizure-induced damage but an MRI study showed that females tend to have less structural atrophy compared to men, regardless of the seizure rate (Briellmann et al., 2000).

Some data on effects of sex and sex steroid hormones on seizure-induced damage can be drawn from animal studies. Sex differences in the response to hormonal treatment have been observed in seizure-induced neuronal damage in the hippocampus. In females, estradiol replacement significantly attenuated hippocampal damage following status epilepticus, while a similar estradiol pretreatment in male rats rather enhanced status epilepticus-associated hippocampal damage (Galanopoulou et al., 2003).

The data on the influence of sex hormones on seizure-induced damage are often misinterpreted. It is critical first to understand the meaning of the word “neuroprotection” in order to correctly interpret the reports on estradiol and progesterone effects on seizure-induced neuronal damage. Seizure-induced damage only occurs if the animals experience severe and prolonged seizures called status epilepticus. The extent of neuronal loss depends on seizure severity as well as duration. Short episodes of seizure activity are not associated with neuronal damage. Thus, when the neuroprotective effects on seizure-induced damage

are examined, it is important to compare only animals with similar seizure duration and severity. In other words, animals that do not experience severe seizures (e.g., because of anticonvulsant effects of a hormonal therapy) do not have neuronal damage and pretreatment with an agent that prevents seizures, has just anticonvulsant but not necessarily neuroprotective effects. This is important for treatment strategies in patients with intractable epilepsies whose seizures are resistant to anticonvulsant therapy but the patients may benefit from treatment with neuroprotective agents. In accordance with these lines, ovariectomized animals pretreated with estradiol and experiencing same seizure duration and severity as untreated ovariectomized controls show significantly reduced neuronal loss in the hippocampus, a region sensitive to seizure-induced damage (Galanopoulou et al., 2003; Hoffman et al., 2003; Reibel et al., 2000; Velíšková and Velíšek, 2007; Velíšková et al., 2000).

The neuroprotective effects of estradiol on seizure-induced damage were linked to regulation of NPY expression (Galanopoulou et al., 2003; Hoffman et al., 2003; Reibel et al., 2000; Velíšková and Velíšek, 2007; Velíšková et al., 2000), enhanced GABA release (Ortiz et al., 2001), and also different neuroprotective molecules [as reviewed in detail elsewhere (Moura and Petersen, 2010; Scott et al., 2011)], may play a role in its robust neuroprotective properties on seizure-induced damage along with mild anticonvulsant effects (Frye and Rhodes, 2005; Hoffman et al., 2003; Reibel et al., 2000; Velíšková et al., 2010; Velíšková and Velíšek, 2007; Velíšková et al., 2000).

Unlike estradiol, progesterone has only anticonvulsant but not neuroprotective effects because in ovariectomized animals pretreated with progesterone and experiencing similar seizure duration and severity as ovariectomized untreated controls, the extent of hippocampal neuronal loss was severe and not different from controls (Hoffman et al., 2003). In addition, several studies showed enhanced expression of steroid-converting enzymes critical for *de novo* brain production of local estradiol but not progesterone by activated microglia (Gottfried-Blackmore et al., 2008; Sierra et al., 2003; Sierra et al., 2008), an effect linked to possible endogenous neuroprotective mechanisms in different neurodegenerative diseases that show activation of microglia such as epilepsy (Vezzani et al., 2011).

Regarding the effects of progesterone on seizure-induced hippocampal damage, no beneficial neuroprotective properties of progesterone or its metabolites have been found even following chronic administration (Hoffman et al., 2003), suggesting that progesterone-mediated genomic effects are not a significant part of neuroprotective mechanisms involved in seizure-induced damage. In addition, progesterone may even counteract the neuroprotective effects of estradiol (Aguirre et al., 2010). Thus, use of progesterone in women with epilepsy seems to be helpful as adjunctive therapy [for review and treatment regimens see (Biagini et al., 2010; Frye, 2010; Herzog, 2009; Reddy, 2010)], mainly to control and correct the hormonal disturbances, which often occur especially in women suffering from temporal lobe epilepsy (Herzog, 1996; Herzog, 2009).

Hormonal changes as a result of epileptiform activity

Both men and women with epilepsy often have altered reproductive function (Herzog et al., 1986a; Herzog et al., 1986b; Sivaraaman and Mintzer, 2011). Steroid hormone levels have been shown to change as a result of seizure activity. Elevations in prolactin and corticosteroids post-seizure are most commonly discussed, attributed to non-specific stress response (Abbott et al., 1980; Duncan, 1957). Here the focus will be more directed towards less commonly discussed changes in other steroid hormones including the sex hormones.

In patients with epilepsy, it is important to first identify the cause of endocrine dysfunction, whether the anticonvulsant treatment or seizure activity itself are responsible for these alterations (Bauer et al., 2002). Numerous studies suggest that anticonvulsant treatments may interfere with endocrine function and reproductive health and that the treatment strategy may need adjustments to alleviate these adverse effects [for review and list of anticonvulsant agents affecting the endocrine system see (Bauer et al., 2002; Harden, 2005; Harden et al., 2010; Tauboll et al., 2008)].

Effects of repeated seizures on hormonal levels and reproductive system have been observed already during prepubescence, although little has been published on this topic. A significant increase in allopregnanolone serum level was observed in both male and female prepubertal children, independent on the type of epilepsy, during the post-ictal phase but not during the inter-ictal phase (Grosso et al., 2005; Grosso et al., 2003).

In prepubescent animals, data regarding changes in reproductive hormonal levels are very limited but suggest that repeated seizure activity leads to endocrine disturbances. For example in rats, there may be delays in onset of puberty possibly related to seizure-induced decrease in prolactin secretion (Bhanot and Wilkinson, 1984; Wilkinson et al., 1982).

In adult women, seizure activity is often associated with irregularities in menstrual cycles and ovarian morphology abnormalities, which are commonly present especially in women with temporal lobe epilepsy (Herzog et al., 1986b; Morrell, 1997). Increased frequency of pulsatile secretion of luteinizing hormone (LH) has been observed in women with epilepsy and may contribute greatly to alterations in ovarian cycle (Bilo et al., 1991; Drislane et al., 1994). Higher LH pulse frequencies positively correlate especially with localization of the focus in the left temporal lobe compared to lower LH pulse frequencies in patients with the right side foci (Drislane et al., 1994). Left temporal lobe seizure origin seems to be more often associated with catamenial pattern of epilepsy and polycystic ovary syndrome (Herzog et al., 1986b; Quigg et al., 2009), a common condition in women with temporal lobe epilepsy (Harden, 2005; Herzog, 1996). On the other hand, the origin of seizure in the right temporal lobe is rather associated with hypogonadotropic hypogonadism and non-catamenial pattern of seizures (Kalinin and Zheleznova, 2007). It was hypothesized that changes in LH pulse frequency occurred possibly due to an alteration in gonadotropin releasing hormone pulse generator as a result of seizure activity (Bilo et al., 1991). A similar pattern of increased pulsatile secretion of gonadotropin releasing hormone leading to increased secretion of LH is generally observed in polycystic ovary syndrome (Burt Solorzano et al., 2011). Finally, seizures also affect levels of allogregnanolone, the seizure-limiting metabolite of progesterone. Allopregnanolone levels were significantly elevated immediately following a seizure and returned back to normal within six hours postictally (Galli et al., 2001).

Animal studies, where clear dissociation between seizure activity and anticonvulsant treatment can be determined, suggest a direct effect of seizure activity in addition to the adverse effects of some anticonvulsants. In models of temporal lobe epilepsy, animals show dysregulation of the estrous cycle and changes in sex hormone levels upon seizures (Amado and Cavalheiro, 1998). Kindling in female rats, specifically in the right amygdala, resulted in cessation of estrous cycles, the animals developed polycystic ovaries, anovulatory cycles, and serum levels of estradiol but not testosterone had risen following several stimulations (Edwards et al., 1999; Edwards et al., 2000; Mejias-Aponte et al., 2002). Exposure of female rats to pilocarpine-induced seizures resulted in increased testosterone levels in conjunction with estrous cycle impairments and development of polycystic ovaries (Scharfman et al., 2008; Scharfman et al., 2009). In a model of primary generalized seizures in female rats, repeated flurothyl-induced seizures induced pseudopregnancy (Bhanot and Wilkinson,

1982). Finally, a recent elegant study showed that in chronically epileptic rats, local neurosteroid production plays an important role as an endogenous seizure-controlling mechanism. Blockade of the neurosteroid synthetic pathway resulted in rapid increase in spontaneous seizure frequency, which could have been remedied with administration of exogenous allopregnanolone (Lawrence et al., 2010).

In men, temporal lobe epilepsy is often associated with reproductive dysfunction and with decreased testosterone levels (Herzog et al., 1986a), and anticonvulsant treatment in men can affect the endocrine function similarly as in women (Harden, 2006; Harden et al., 2010). Altered LH pulses have been recorded in men with mesial temporal lobe epilepsy, in a study examining both acute seizures and chronic epilepsy (Quigg et al., 2002). Measurements of LH were taken both prior to and every ten minutes after seizure. Interestingly, results indicated a decrease in LH pulse frequency in both acute seizures and in the chronic epilepsy group. This finding is in direct contrast to previously published data showing an increase in LH pulse frequency in men post temporal lobe seizure (Herzog et al., 1990); however, both groups of investigators agree that seizure activity leads to a distinct impairment of regulation in the pulse frequency of LH in men.

In males, fewer animal studies on effects of seizures on endocrine function and sex hormone levels have been done compared to females. Available data, however, confirm that in male rats (similar to females), seizure activity itself also leads to alterations in the reproductive system. For example in male rats, repeated electroshock or kainic acid-induced seizures were associated with hypogonadism and decreased testosterone levels (Edwards et al., 2000; Mejias-Aponte et al., 2002), while right amygdala kindling resulted in increased prolactin, testosterone, and estradiol levels (Edwards et al., 2000). These data suggest that the hypothalamic-pituitary-gonadal axis is altered by seizures, especially originating from the right amygdala.

Conclusions

It is clear from clinical studies that a subpopulation of patients with epilepsy has enhanced sensitivity of seizure attacks to hormonal milieu and in turn endocrine function is affected by seizures. This alteration in endocrine function is especially seen in patients with temporal lobe epilepsy. Animal studies reveal that effects of reproductive hormones on neuronal excitability, seizures, and seizure-induced damage are complex because of the multifaceted action of steroid hormones, which induce genomic effects involving modulation of multiple genes by their up- or down-regulation and rapid non-genomic effects by activation of membrane orphan G-protein coupled receptors, specific membrane hormone receptors, or by direct binding to neurotransmitter receptors. Available data especially regarding the effects of estradiol unfortunately lack consistency in experimental design making the comparisons among the studies extremely difficult. Such absence of comparable data limits the possibility to follow a specific pathway involved in the effect of estradiol on neuronal excitability. In addition, there is a common belief that estradiol has proconvulsant effects while progesterone is anticonvulsant, which often leads investigators to selective analyses of their data in favor of such preconception. Thus, more studies using rigorous and consistent treatment paradigms taking into consideration the fact, that sex hormones may have biphasic dose-dependent action with beneficial effects of doses within physiological range and possible adverse effects of supraphysiological doses, are necessary.

In conclusion, we would like to suggest that both estradiol and progesterone/allopregnanolone might provide beneficial effects for patients with epilepsy. Progesterone and its metabolite allopregnanolone may help to limit seizure activity but progesterone has no confirmed neuroprotective properties against seizure-induced damage. Long-term

administration of progesterone or its metabolites may lead to development of tolerance and paradoxical enhancement of neuronal excitability. Estradiol may be less effective as anticonvulsant agent compared to progesterone but it can protect hippocampal neurons against seizure-induced damage. If hormonal therapy is considered as adjunctive treatment in patients with epilepsy to improve seizure control as well as quality of life, individualized treatment strategy is critical including adjustments in doses of both anticonvulsants and the hormones to prevent adverse outcomes.

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References

Abbasi F, Krumholz A, Kittner SJ, Langenberg P. Effects of menopause on seizures in women with epilepsy. Epilepsia. 1999; 40:205–10. [PubMed: 9952268]

Abbott RJ, Browning MC, Davidson DL. Serum prolactin and cortisol concentrations after grand mal seizures. J Neurol Neurosurg Psychiatry. 1980; 43:163–7. [PubMed: 6766989]

Aguirre C, Jayaraman A, Pike C, Baudry M. Progesterone inhibits estrogen-mediated neuroprotection against excitotoxicity by down-regulating estrogen receptor-beta. J Neurochem. 2010; 115:1277–87. [PubMed: 20977477]

Amado D, Cavalheiro EA. Hormonal and gestational parameters in female rats submitted to the pilocarpine model of epilepsy. Epilepsy Res. 1998; 32:266–74. [PubMed: 9761326]

Backstrom T. Epileptic seizures in women related to plasma estrogen and progesterone during the menstrual cycle. Acta Neurol Scand. 1976; 54:321–47. [PubMed: 973554]

Bandler B, Dykens JW, Kaufman IC, Schleifer M, Shapiro LN. Seizures and the menstrual cycle. Am J Psychiatry. 1957; 113:704–8. [PubMed: 13394744]

Barker JM, Galea LA. Sex and regional differences in estradiol content in the prefrontal cortex, amygdala and hippocampus of adult male and female rats. Gen Comp Endocrinol. 2009; 164:77–84. [PubMed: 19457436]

Bauer J. Catamenial epilepsy and menopause. Epilepsia. 2001a; 42:572. [PubMed: 11440355]

Bauer J. Interactions between hormones and epilepsy in female patients. Epilepsia. 2001b; 42(Suppl 3):20–2. [PubMed: 11520317]

Bauer J, Isojarvi JI, Herzog AG, Reuber M, Polson D, Tauboll E, Genton P, van der Ven H, Roesing B, Luef GJ, Galimberti CA, van Parys J, Flugel D, Bergmann A, Elger CE. Reproductive dysfunction in women with epilepsy: recommendations for evaluation and management. J Neurol Neurosurg Psychiatry. 2002; 73:121–5. [PubMed: 12122167]

Berzaghi Mda P, Amado D, Cavalheiro EA. Pregnancy decreases the frequency of spontaneous recurrent seizures in rats with kainic acid lesions of the hippocampus. Epilepsy Res. 1987; 1:142–4. [PubMed: 3504390]

Bhanot R, Wilkinson M. Repeated convulsions induce pseudopregnancy in the intact rat and inhibit steroid-mediated gonadotrophin secretion in the ovariectomized rat. J Endocrinol. 1982; 95:43–8. [PubMed: 6813416]

Bhanot R, Wilkinson M. Differential effects of flurothyl- and electro-convulsive shock on sexual maturation and prolactin release in the rat. Exp Brain Res. 1984; 56:32–9. [PubMed: 6432572]

Biagini G, Panuccio G, Avoli M. Neurosteroids and epilepsy. Curr Opin Neurol. 2010; 23:170–6. [PubMed: 20160650]

Bilo L, Meo R, Valentino R, Buscaino GA, Striano S, Nappi C. Abnormal pattern of luteinizing hormone pulsatility in women with epilepsy. Fertil Steril. 1991; 55:705–11. [PubMed: 1901278]

Bohacek J, Bearl AM, Daniel JM. Long-term ovarian hormone deprivation alters the ability of subsequent oestradiol replacement to regulate choline acetyltransferase protein levels in the hippocampus and prefrontal cortex of middle-aged rats. J Neuroendocrinol. 2008; 20:1023–7. [PubMed: 18540996]

Bohacek J, Daniel JM. The ability of oestradiol administration to regulate protein levels of oestrogen receptor alpha in the hippocampus and prefrontal cortex of middle-aged rats is altered following long-term ovarian hormone deprivation. J Neuroendocrinol. 2009; 21:640–7. [PubMed: 19453823]

Briellmann RS, Berkovic SF, Jackson GD. Men may be more vulnerable to seizure-associated brain damage. Neurology. 2000; 55:1479–85. [PubMed: 11094101]

Burakgazi E, Pollard J, Harden C. The effect of pregnancy on seizure control and antiepileptic drugs in women with epilepsy. Rev Neurol Dis. 2011; 8:16–22. [PubMed: 21769067]

Burt Solorzano CM, Beller JP, Abshire MY, Collins JS, McCartney CR, Marshall JC. Neuroendocrine dysfunction in polycystic ovary syndrome. Steroids. 2011

Christensen J, Kjeldsen MJ, Andersen H, Friis ML, Sidenius P. Gender differences in epilepsy. Epilepsia. 2005; 46:956–60. [PubMed: 15946339]

Clarke M, Gill J, Noronha M, McKinlay I. Early infantile epileptic encephalopathy with suppression burst: Ohtahara syndrome. Dev Med Child Neurol. 1987; 29:520–8. [PubMed: 3678631]

Cramer JA, Gordon J, Schachter S, Devinsky O. Women with epilepsy: hormonal issues from menarche through menopause. Epilepsy Behav. 2007; 11:160–78. [PubMed: 17662661]

do Vale TG, da Silva AV, Lima DC, de Lima E, Torres LB, Cossa AC, de Oliveira EM, Cabral FR, Cavalheiro EA, Naffah-Mazzacoratti Mda G, Amado D. Seizures during pregnancy modify the development of hippocampal interneurons of the offspring. Epilepsy Behav. 2010; 19:20–5. [PubMed: 20708978]

Drislane FW, Coleman AE, Schomer DL, Ives J, Levesque LA, Seibel MM, Herzog AG. Altered pulsatile secretion of luteinizing hormone in women with epilepsy. Neurology. 1994; 44:306–10. [PubMed: 8309580]

Duncan IW. The effect of audiogenic seizures in rats on the adrenal weight, ascorbic acid, cholesterol, and corticosteroids. J Biol Chem. 1957; 229:563–8. [PubMed: 13502319]

Edwards HE, Burnham WM, Ng MM, Asa S, MacLusky NJ. Limbic seizures alter reproductive function in the female rat. Epilepsia. 1999; 40:1370–7. [PubMed: 10528931]

Edwards HE, MacLusky NJ, Burnham WM. The effect of seizures and kindling on reproductive hormones in the rat. Neurosci Biobehav Rev. 2000; 24:753–62. [PubMed: 10974355]

Engel, J., Jr; Williamson, PD.; Wieser, H-G. Mesial temporal lobe epilepsy. In: Engel, J., Jr; Pedley, TA., editors. Epilepsy: A Comprehensive Textbook. Lippincot-Raven Publishers; Philadelphia: 1997. p. 2417-2426.

Forsgren L, Sidenvall R, Blomquist HK, Heijbel J. A prospective incidence study of febrile convulsions. Acta paediatrica Scandinavica. 1990; 79:550–7. [PubMed: 2386045]

Foy MR, Baudry M, Akopian GK, Thompson RF. Regulation of hippocampal synaptic plasticity by estrogen and progesterone. Vitam Horm. 2010; 82:219–39. [PubMed: 20472141]

Frye CA. Role of androgens in epilepsy. Expert Rev Neurother. 2006; 6:1061–75. [PubMed: 16831119]

Frye CA. Effects and mechanisms of progestogens and androgens in ictal activity. Epilepsia. 2010; 51(Suppl 3):135–40. [PubMed: 20618419]

Frye CA, Bayon LE. Cyclic withdrawal from endogenous and exogenous progesterone increases kainic acid and perforant pathway induced seizures. Pharmacol Biochem Behav. 1999; 62:315–21. [PubMed: 9972699]

Frye CA, Manjarrez J, Camacho-Arroyo I. Infusion of 3alpha,5alpha-THP to the pontine reticular formation attenuates PTZ-induced seizures [In Process Citation]. Brain Res. 2000; 881:98–102. [PubMed: 11033099]

Frye CA, Rhodes ME. Estrogen-priming can enhance progesterone's anti-seizure effects in part by increasing hippocampal levels of allopregnanolone. Pharmacol Biochem Behav. 2005; 81:907–16. [PubMed: 16085296]

Frye CA, Rhodes ME, Walf A, Harney J. Progesterone reduces pentylenetetrazol-induced ictal activity of wild-type mice but not those deficient in type I 5alpha-reductase. Epilepsia. 2002; 43(Suppl 5): 14–7. [PubMed: 12121288]

Frye CA, Walf A. Progesterone, administered before kainic acid, prevents decrements in cognitive performance in the Morris Water Maze. Dev Neurobiol. 2011; 71:142–52. [PubMed: 20715152]

Galanopoulou AS, Alm EM, Velíšková J. Estradiol reduces seizure-induced hippocampal injury in ovariectomized female but not in male rats. Neurosci Lett. 2003; 342:201–5. [PubMed: 12757899]

Galli R, Luisi M, Pizzanelli C, Monteleone P, Casarosa E, Iudice A, Murri L. Circulating levels of allopregnanolone, an anticonvulsant metabolite of progesterone, in women with partial epilepsy in the postcritical phase. Epilepsia. 2001; 42:216–9. [PubMed: 11240592]

Gevorkyan ES, Nazaryan KB, Kostanyan AA. Modifying effect of estradiol and progesterone on epileptic activity of the rat brain. Neurosci Behav Physiol. 1989; 19:412–5. [PubMed: 2533330]

Giuliani FA, Yunes R, Mohn CE, Laconi M, Rettori V, Cabrera R. Allopregnanolone induces LHRH and glutamate release through NMDA receptor modulation. Endocrine. 2011; 40:21–6. [PubMed: 21455639]

Gordon A. Epilepsy in its relation to menstrual periods. NY Med J. 1909; XC:733–35.

Gottfried-Blackmore A, Sierra A, Jellinck PH, McEwen BS, Bulloch K. Brain microglia express steroid-converting enzymes in the mouse. J Steroid Biochem Mol Biol. 2008; 109:96–107. [PubMed: 18329265]

Grosso S, Luisi S, Berardi R, Mostardini R, Cordelli DM, Morgese G, Petraglia F, Balestri P. Post-ictal circulating levels of allopregnanolone in children with partial or generalized seizures. Epilepsy Res. 2005; 63:97–102. [PubMed: 15725389]

Grosso S, Luisi S, Mostardini R, Farnetani M, Cobellis L, Morgese G, Balestri P, Petraglia F. Inter-ictal and post-ictal circulating levels of allopregnanolone, an anticonvulsant metabolite of progesterone, in epileptic children. Epilepsy Res. 2003; 54:29–34. [PubMed: 12742593]

Guerrero R, Aso T, Brenner PF, Cekan Z, Landgren BM, Hagenfeldt K, Diczfalusy E. Studies on the pattern of circulating steroids in the normal menstrual cycle. I. Simultaneous assays of progesterone, pregnenolone, dehydroepiandrosterone, testosterone, dihydrotestosterone, androstenedione, oestradiol and oestrone. Acta Endocrinol (Copenh). 1976; 81:133–49. [PubMed: 128969]

Harden C, MacLusky NJ. Aromatase inhibitors as add-on treatment for men with epilepsy. Expert Rev Neurother. 2005; 5:123–7. [PubMed: 15853482]

Harden CL. Polycystic ovaries and polycystic ovary syndrome in epilepsy: evidence for neurogonadal disease. Epilepsy Curr. 2005; 5:142–6. [PubMed: 16151523]

Harden CL. Sexuality in men and women with epilepsy. CNS Spectr. 2006; 11:13–8. [PubMed: 16871133]

Harden CL. Hormone replacement therapy: will it affect seizure control and AED levels? Seizure. 2008; 17:176–80. [PubMed: 18187348]

Harden CL, Herzog AG, Nikolov BG, Koppel BS, Christos PJ, Fowler K, Labar DR, Hauser WA. Hormone replacement therapy in women with epilepsy: a randomized, double-blind, placebo-controlled study. Epilepsia. 2006; 47:1447–51. [PubMed: 16981859]

Harden CL, Koppel BS, Herzog AG, Nikolov BG, Hauser WA. Seizure frequency is associated with age at menopause in women with epilepsy. Neurology. 2003; 61:451–5. [PubMed: 12939416]

Harden CL, Nikolov BG, Kandula P, Labar DR, Pannullo S. Effect of levetiracetam on testosterone levels in male patients. Epilepsia. 2010; 51:2348–51. [PubMed: 21175608]

Harden CL, Pulver MC, Ravdin L, Jacobs AR. The effect of menopause and perimenopause on the course of epilepsy. Epilepsia. 1999; 40:1402–7. [PubMed: 10528936]

Hauser WA, Annegers JF, Kurland LT. Prevalence of epilepsy in Rochester, Minnesota: 1940–1980. Epilepsia. 1991; 32:429–45. [PubMed: 1868801]

Herzog AG. Polycystic ovarian syndrome in women with epilepsy: epileptic or iatrogenic? Ann Neurol. 1996; 39:559–60. [PubMed: 8619539]

Herzog AG. Psychoneuroendocrine aspects of temporolimbic epilepsy. Part II: Epilepsy and reproductive steroids. Psychosomatics. 1999; 40:102–8. [PubMed: 10100431]

Herzog AG. Hormonal therapies: progesterone. Neurotherapeutics. 2009; 6:383–91. [PubMed: 19332334]

Herzog AG, Drislane FW, Schomer DL, Levesque LA, Ives J, Blume HW, Dubuisson D, Cosgrove GR. Abnormal pulsatile secretion of luteinizing hormone in men with epilepsy: relationship to laterality and nature of paroxysmal discharges. Neurology. 1990; 40:1557–61. [PubMed: 2215947]

Herzog AG, Frye CA. Seizure exacerbation associated with inhibition of progesterone metabolism. Ann Neurol. 2003; 53:390–1. [PubMed: 12601707]

Herzog AG, Klein P, Ransil BJ. Three patterns of catamenial epilepsy. Epilepsia. 1997; 38:1082–8. [PubMed: 9579954]

Herzog AG, Seibel MM, Schomer D, Vaitukaitis J, Geschwind N. Temporal lobe epilepsy: an extrahypothalamic pathogenesis for polycystic ovarian syndrome? Neurology. 1984; 34:1389–93. [PubMed: 6541317]

Herzog AG, Seibel MM, Schomer DL, Vaitukaitis JL, Geschwind N. Reproductive endocrine disorders in men with partial seizures of temporal lobe origin. Arch Neurol. 1986a; 43:347–50. [PubMed: 3082313]

Herzog AG, Seibel MM, Schomer DL, Vaitukaitis JL, Geschwind N. Reproductive endocrine disorders in women with partial seizures of temporal lobe origin. Arch Neurol. 1986b; 43:341–6. [PubMed: 2937394]

Hoffman GE, Moore N, Fiskum G, Murphy AZ. Ovarian steroid modulation of seizure severity and hippocampal cell death after kainic acid treatment. Exp Neurol. 2003; 182:124–34. [PubMed: 12821382]

Jacono JJ, Robertson JMD. The effects of estrogen, progesterone, and ionized calcium on seizures during the menstrual cycle of epileptic women. Epilepsia. 1987; 28:571–577. [PubMed: 3653063]

Janszky J, Schulz R, Janszky I, Ebner A. Medial temporal lobe epilepsy: gender differences. J Neurol Neurosurg Psychiatry. 2004; 75:773–5. [PubMed: 15090578]

Jensen EV, Jacobson HI, Walf AA, Frye CA. Estrogen action: a historic perspective on the implications of considering alternative approaches. Physiol Behav. 2010; 99:151–62. [PubMed: 19737574]

Joshi S, Rajasekaran K, Kapur J. GABAergic transmission in temporal lobe epilepsy: The role of neurosteroids. Exp Neurol. 2011

Kalinin VV, Zheleznova EV. Chronology and evolution of temporal lobe epilepsy and endocrine reproductive dysfunction in women: relationships to side of focus and catameniality. Epilepsy Behav. 2007; 11:185–91. [PubMed: 17573242]

Kalkbrenner KA, Standley CA. Estrogen modulation of NMDA-induced seizures in ovariectomized and non-ovariectomized rats. Brain Res. 2003; 964:244–9. [PubMed: 12576185]

Klein P, Serje A, Pezzullo JC. Premature ovarian failure in women with epilepsy. Epilepsia. 2001; 42:1584–9. [PubMed: 11879371]

Klein P, van Passel-Clark LM, Pezzullo JC. Onset of epilepsy at the time of menarche. Neurology. 2003; 60:495–7. [PubMed: 12578935]

Konkle AT, McCarthy MM. Developmental time course of estradiol, testosterone, and dihydrotestosterone levels in discrete regions of male and female rat brain. Endocrinology. 2011; 152:223–35. [PubMed: 21068160]

Koonce CJ, Walf AA, Frye CA. Type 1 5alpha-reductase may be required for estrous cycle changes in affective behaviors of female mice. Behav Brain Res. 2012; 226:376–80. [PubMed: 21946309]

Laidlaw J. Catamenial epilepsy. Lancet. 1956; 2:1235–1237. [PubMed: 13386215]

Lambert JJ, Cooper MA, Simmons RD, Weir CJ, Belelli D. Neurosteroids: endogenous allosteric modulators of GABA(A) receptors. Psychoneuroendocrinology. 2009; 34(Suppl 1):S48–58. [PubMed: 19758761]

Larner AJ. Epileptic seizures in AD patients. Neuromolecular Med. 2010; 12:71–7. [PubMed: 19557550]

Lavaque E, Sierra A, Azcoitia I, Garcia-Segura LM. Steroidogenic acute regulatory protein in the brain. Neuroscience. 2006; 138:741–7. [PubMed: 16338087]

Lawrence C, Martin BS, Sun C, Williamson J, Kapur J. Endogenous neurosteroid synthesis modulates seizure frequency. Ann Neurol. 2010; 67:689–93. [PubMed: 20437568]

Ledoux VA, Smejkalova T, May RM, Cooke BM, Woolley CS. Estradiol facilitates the release of neuropeptide Y to suppress hippocampus-dependent seizures. J Neurosci. 2009; 29:1457–68. [PubMed: 19193892]

Lima DC, Vale TG, Arganaraz GA, Varella PP, Frussa-Filho R, Cavalheiro EA, Naffah-Mazzacoratti Mda G, Amado D. Behavioral evaluation of adult rats exposed in utero to maternal epileptic seizures. Epilepsy Behav. 2010; 18:45–9. [PubMed: 20460194]

Lonsdale D, Nylen K, McIntyre Burnham W. The anticonvulsant effects of progesterone and its metabolites on amygdala-kindled seizures in male rats. Brain Res. 2006; 1101:110–6. [PubMed: 16784731]

Luchetti S, Huitinga I, Swaab DF. Neurosteroid and GABA-A receptor alterations in Alzheimer's disease, Parkinson's disease and multiple sclerosis. Neuroscience. 2011; 191:6–21. [PubMed: 21514366]

Lukkes JL, Engelman GH, Zelin NS, Hale MW, Lowry CA. Post-weaning social isolation of female rats, anxiety-related behavior, and serotonergic systems. Brain Res. 2012; 1443:1–17. [PubMed: 22297173]

Luthvigsson P, Olafsson E, Sigurthardottir S, Hauser WA. Epidemiologic features of infantile spasms in Iceland. Epilepsia. 1994; 35:802–5. [PubMed: 8082625]

Majewska MD. Neurosteroids: Endogenous bimodal modulators of the GABAA receptor. Mechanism of action and physiological significance. Progr Neurobiol. 1992; 38:379–395.

Mathern GW, Babb TL, Leite JP, Pretorius K, Yeoman KM, Kuhlman PA. The pathogenic and progressive features of chronic human hippocampal epilepsy. Epilepsy Res. 1996; 26:151–61. [PubMed: 8985697]

McCarthy MM, Arnold AP. Reframing sexual differentiation of the brain. Nat Neurosci. 2011; 14:677–83. [PubMed: 21613996]

McEwen B. Estrogen actions throughout the brain. Recent Prog Horm Res. 2002; 57:357–84. [PubMed: 12017552]

McHugh JC, Delanty N. Epidemiology and classification of epilepsy: gender comparisons. Int Rev Neurobiol. 2008; 83:11–26. [PubMed: 18929074]

Mejias-Aponte CA, Jimenez-Rivera CA, Segarra AC. Sex differences in models of temporal lobe epilepsy: role of testosterone. Brain Res. 2002; 944:210–8. [PubMed: 12106683]

Miranda P, Williams CL, Einstein G. Granule cells in aging rats are sexually dimorphic in their response to estradiol. J Neurosci. 1999; 19:3316–25. [PubMed: 10212291]

Morali G, Montes P, Gonzalez-Burgos I, Velazquez-Zamora DA, Cervantes M. Cytoarchitectural characteristics of hippocampal CA1 pyramidal neurons of rats, four months after global cerebral ischemia and progesterone treatment. Restor Neurol Neurosci. 2012; 30:1–8. [PubMed: 22377905]

Moran MH, Smith SS. Progesterone withdrawal I: pro-convulsant effects. Brain Res. 1998; 807:84–90. [PubMed: 9757004]

Morrell MJ. Hormones and epilepsy through the lifetime. Epilepsia. 1992; 33:S49–61. [PubMed: 1425494]

Morrell MJ. Antiepileptic drugs, seizures, and birth defects. International Pediatrics. 1995; 10:58–65.

Morrell, MJ. Hormones Reproductive Health, and Epilepsy. In: Wyllie, E., editor. The Treatment of Epilepsy: Principles and Practice. Williams & Wilkins; Baltimore: 1997. p. 179-187.

Morrell MJ. Pregnancy and antiepileptic drugs. Curr Neurol Neurosci Rep. 2001; 1:359–60. [PubMed: 11898542]

Moura PJ, Petersen SL. Estradiol acts through nuclear- and membrane-initiated mechanisms to maintain a balance between GABAergic and glutamatergic signaling in the brain: implications for hormone replacement therapy. Rev Neurosci. 2010; 21:363–80. [PubMed: 21280455]

Mouridsen SE. The Landau-Kleffner Syndrome: a review. Eur Child Adolesc Psychiatry. 1995; 4:223–8. [PubMed: 8608387]

Nakamura NH, McEwen BS. Changes in interneuronal phenotypes regulated by estradiol in the adult rat hippocampus: a potential role for neuropeptide Y. Neuroscience. 2005; 136:357–69. [PubMed: 16198490]

Nakamura NH, Rosell DR, Akama KT, McEwen BS. Estrogen and ovariectomy regulate mRNA and protein of glutamic acid decarboxylases and cation-chloride cotransporters in the adult rat hippocampus. Neuroendocrinology. 2004; 80:308–23. [PubMed: 15677881]

Nakamura NH, Rosell DR, Akama KT, McEwen BS. Estrogen and Ovariectomy Regulate mRNA and Protein of Glutamic Acid Decarboxylases and Cation-Chloride Cotransporters in the Adult Rat Hippocampus. Neuroendocrinology. 2005; 80:308–323. [PubMed: 15677881]

Neal-Perry GS, Zeevalk GD, Santoro NF, Etgen AM. Attenuation of preoptic area glutamate release correlates with reduced luteinizing hormone secretion in middle-aged female rats. Endocrinology. 2005; 146:4331–9. [PubMed: 15994345]

Newmark ME, Penry JK. Catamenial epilepsy: a review. Epilepsia. 1980; 21:281–300. [PubMed: 6991251]

Nicoletti F, Speciale C, Sortino MA, Summa G, Caruso G, Patti F, Canonico PL. Comparative effects of estradiol benzoate, the antiestrogen clomiphene citrate, and the progestin medroxyprogesterone acetate on kainic acid-induced seizures in male and female rats. Epilepsia. 1985; 26:252–257. [PubMed: 3159567]

Nordli DR Jr. Idiopathic generalized epilepsies recognized by the International League Against Epilepsy. Epilepsia. 2005; 46(Suppl 9):48–56. [PubMed: 16302875]

Novaes GF, Amado D, Scorza FA, Cysneiros RM. Social behavior impairment in offspring exposed to maternal seizures in utero. J Neural Transm. 2012

Ortiz GG, Sanchez-Ruiz Y, Tan DX, Reiter RJ, Benitez-King G, Beas-Zarate C. Melatonin, vitamin E, and estrogen reduce damage induced by kainic acid in the hippocampus: potassium-stimulated GABA release. J Pineal Res. 2001; 31:62–7. [PubMed: 11485006]

Osborne DM, Frye CA. Estrogen increases latencies to seizures and levels of 5alpha-pregnan-3alpha-ol-20-one in hippocampus of wild-type, but not 5alpha-reductase knockout, mice. Epilepsy Behav. 2009; 16:411–4. [PubMed: 19782646]

Pack AM. Treatment of epilepsy to optimize bone health. Curr Treat Options Neurol. 2011; 13:346–54. [PubMed: 21557040]

Peebles CT, McAuley JW, Moore JL, Malone HJ, Reeves AL. Hormone replacement therapy in a postmenopausal woman with epilepsy. Ann Pharmacother. 2000; 34:1028–31. [PubMed: 10981250]

Pennell PB. Pregnancy in women who have epilepsy. Neurol Clin. 2004; 22:799–820. [PubMed: 15474768]

Pericic D, Bujas M. Sex differences in bicuculline-induced convulsions: interaction with stress and ligands of benzodiazepine binding sites. Brain Research. 1997a; 752:279–84. [PubMed: 9106468]

Pericic D, Bujas M. Sex differences in the response to GABA antagonists depend on the route of drug administration. Exp Brain Res. 1997b; 115:187–90. [PubMed: 9224848]

Pericic D, Manev H, Geber J. Sex-related differences in the response of mice, rats and cats to the administration of picrotoxin. Life Sci. 1986; 38:905–913. [PubMed: 3951316]

Pericic D, Manev H, Lakic N. Sex differences in the response of rats to drugs affecting GABAergic transmission. Life Sci. 1985; 36:541–547. [PubMed: 2982069]

Quigg M, Kiely JM, Shneker B, Veldhuis JD, Bertram EH 3rd. Interictal and postictal alterations of pulsatile secretions of luteinizing hormone in temporal lobe epilepsy in men. Ann Neurol. 2002; 51:559–66. [PubMed: 12112101]

Quigg M, Smithson SD, Fowler KM, Sursal T, Herzog AG. Laterality and location influence catamenial seizure expression in women with partial epilepsy. Neurology. 2009; 73:223–7. [PubMed: 19620611]

Raffo E, de Vasconcelos AP, Boehrer A, Desor D, Nehlig A. Neurobehavioral maturation of offspring from epileptic dams: study in the rat lithium-pilocarpine model. Exp Neurol. 2009; 219:414–23. [PubMed: 19563803]

Reddy DS. The role of neurosteroids in the pathophysiology and treatment of catamenial epilepsy. Epilepsy Res. 2009; 85:1–30. [PubMed: 19406620]

Reddy DS. Neurosteroids: endogenous role in the human brain and therapeutic potentials. Prog Brain Res. 2010; 186:113–37. [PubMed: 21094889]

Reddy DS, Mohan A. Development and persistence of limbic epileptogenesis are impaired in mice lacking progesterone receptors. J Neurosci. 2011; 31:650–8. [PubMed: 21228174]

Reddy DS, Rogawski MA. Enhanced anticonvulsant activity of neuroactive steroids in a rat model of catamenial epilepsy. Epilepsia. 2001; 42:337–44. [PubMed: 11442150]

Reddy DS, Rogawski MA. Neurosteroid replacement therapy for catamenial epilepsy. Neurotherapeutics. 2009; 6:392–401. [PubMed: 19332335]

Redei E, Freeman EW. Daily plasma estradiol and progesterone levels over the menstrual cycle and their relation to premenstrual symptoms. Psychoneuroendocrinology. 1995; 20:259–67. [PubMed: 7777654]

Reibel S, Andre V, Chassagnon S, Andre G, Marescaux C, Nehlig A, Depaulis A. Neuroprotective effects of chronic estradiol benzoate treatment on hippocampal cell loss induced by status epilepticus in the female rat. Neurosci Lett. 2000; 281:79–82. [PubMed: 10704747]

Ryan SG, Chance PF, Zou CH, Spinner NB, Golden JA, Smietana S. Epilepsy and mental retardation limited to females: an X-linked dominant disorder with male sparing. Nat Genet. 1997; 17:92–5. [PubMed: 9288105]

Sachs M, Pape HC, Speckmann EJ, Gorji A. The effect of estrogen and progesterone on spreading depression in rat neocortical tissues. Neurobiol Dis. 2007; 25:27–34. [PubMed: 17008106]

Savic I, Engel J Jr. Sex differences in patients with mesial temporal lobe epilepsy. J Neurol Neurosurg Psychiatry. 1998; 65:910–2. [PubMed: 9854969]

Scharfman HE, Goodman JH, Rigoulot MA, Berger RE, Walling SG, Mercurio TC, Stormes K, Maclusky NJ. Seizure susceptibility in intact and ovariectomized female rats treated with the convulsant pilocarpine. Exp Neurol. 2005; 196:73–86. [PubMed: 16084511]

Scharfman HE, Kim M, Hintz TM, MacLusky NJ. Seizures and reproductive function: insights from female rats with epilepsy. Ann Neurol. 2008; 64:687–97. [PubMed: 19107990]

Scharfman HE, MacLusky NJ. The influence of gonadal hormones on neuronal excitability, seizures, and epilepsy in the female. Epilepsia. 2006; 47:1423–40. [PubMed: 16981857]

Scharfman HE, Malthankar-Phatak GH, Friedman D, Pearce P, McCloskey DP, Harden CL, Maclusky NJ. A rat model of epilepsy in women: a tool to study physiological interactions between endocrine systems and seizures. Endocrinology. 2009; 150:4437–42. [PubMed: 19443573]

Schmidt, D. The effect of pregnancy on the natural history of epilepsy: review of the literature. In: Janz, D.; Dam, M.; Richens, A.; Bossi, L., editors. Epilepsy, Pregnancy and Child. Raven Press; New York: 1982. p. 3-14.

Schwartz-Giblin S, Korotzer A, Pfaff DW. Steroid hormone effects on picrotoxin-induced seizures in female and male rats. Brain Res. 1989; 476:240–247. [PubMed: 2702466]

Scott E, Zhang QG, Wang R, Vadlamudi R, Brann D. Estrogen neuroprotection and the critical period hypothesis. Front Neuroendocrinol. 2011

Sierra A, Azcoitia I, Garcia-Segura L. Endogenous estrogen formation is neuroprotective in model of cerebellar ataxia. Endocrine. 2003; 21:43–51. [PubMed: 12777702]

Sierra A, Gottfried-Blackmore A, Milner TA, McEwen BS, Bulloch K. Steroid hormone receptor expression and function in microglia. Glia. 2008; 56:659–74. [PubMed: 18286612]

Sivaraaman K, Mintzer S. Hormonal consequences of epilepsy and its treatment in men. Curr Opin Endocrinol Diabetes Obes. 2011; 18:204–9. [PubMed: 21478749]

Šlamberová R, Schindler CJ, Vathy I. Impact of maternal morphine and saline injections on behavioral responses to a cold water stressor in adult male and female progeny. Physiol Behav. 2002; 75:723–32. [PubMed: 12020737]

Šlamberová R, Vathy I. Estrogen differentially alters NMDA- and kainate-induced seizures in prenatally morphine- and saline-exposed adult female rats. Pharmacol Biochem Behav. 2000; 67:501–5. [PubMed: 11164079]

Smith MS, Freeman ME, Neill JD. The control of progesterone secretion during the estrous cycle and early pseudopregnancy in the rat: prolactin, gonadotropin and steroid levels associated with rescue of the corpus luteum of pseudopregnancy. Endocrinology. 1975; 96:219–26. [PubMed: 1167352]

Smith SS, Shen H, Gong QH, Zhou X. Neurosteroid regulation of GABA(A) receptors: Focus on the alpha4 and delta subunits. Pharmacol Ther. 2007; 116:58–76. [PubMed: 17512983]

Spencer JL, Waters EM, Romeo RD, Wood GE, Milner TA, McEwen BS. Uncovering the mechanisms of estrogen effects on hippocampal function. Front Neuroendocrinol. 2008; 29:219–37. [PubMed: 18078984]

Sperk G, Hamilton T, Colmers WF. Neuropeptide Y in the dentate gyrus. Prog Brain Res. 2007; 163:285–97. [PubMed: 17765725]

Stoffel-Wagner B, Beyenburg S, Watzka M, Blumcke I, Bauer J, Schramm J, Bidlingmaier F, Elger CE. Expression of 5alpha-reductase and 3alpha-hydroxisteroid oxidoreductase in the hippocampus of patients with chronic temporal lobe epilepsy. Epilepsia. 2000; 41:140–7. [PubMed: 10691110]

Tauboll E, Roste LS, Svalheim S, Gjerstad L. Disorders of reproduction in epilepsy--what can we learn from animal studies? Seizure. 2008; 17:120–6. [PubMed: 18155932]

Taylor DC. Differential rates of cerebral maturation between sexes and between hemisheres: Evidence for epilepsy. Lancet. 1969; 2:140–2. [PubMed: 4183249]

Teyler TJ, Vardaris RM, Lewis D, Rawitch AB. Gonadal steroids: Effects on excitability of hippocampal pyramidal cells. Science. 1980; 209:1017–19. [PubMed: 7190730]

Thielen RJ, McBride WJ, Lumeng L, Li TK. Housing conditions alter GABAA receptor of alcohol-preferring and -nonpreferring rats. Pharmacol Biochem Behav. 1993; 46:723–7. [PubMed: 8278451]

Thomas J. Gender difference in susceptibility to picrotoxin-induced seizures is seizure- and stimulation-dependent. Brain Res Bull. 1990; 24:7–10. [PubMed: 2310947]

Tominaga K, Yamauchi A, Shuto H, Niizeki M, Makino K, Oishi R, Kataoka Y. Ovariectomy aggravates convulsions and hippocampal gamma-aminobutyric acid inhibition induced by cyclosporin A in rats. Eur J Pharmacol. 2001; 430:243–9. [PubMed: 11711037]

Tomson T, Battino D. Pregnancy and epilepsy: what should we tell our patients? J Neurol. 2009a; 256:856–62. [PubMed: 19252776]

Tomson T, Battino D. Teratogenic effects of antiepileptic medications. Neurol Clin. 2009b; 27:993–1002. [PubMed: 19853219]

Tomson T, Battino D. Antiepileptic treatment in pregnant women: morphological and behavioural effects. Handb Exp Pharmacol. 2011; 205:295–315. [PubMed: 21882118]

Toran-Allerand CD. Minireview: A plethora of estrogen receptors in the brain: where will it end? Endocrinology. 2004; 145:1069–74. [PubMed: 14670986]

Trevathan E, Murphy CC, Yeargin-Allsopp M. Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. Epilepsia. 1997; 38:1283–8. [PubMed: 9578523]

Tsuboi T. Epidemiology of febrile and afebrile convulsions in children in Japan. Neurology. 1984; 34:175–81. [PubMed: 6538005]

Turkmen S, Backstrom T, Wahlstrom G, Andreen L, Johansson IM. Tolerance to allopregnanolone with focus on the GABA-A receptor. Br J Pharmacol. 2011; 162:311–27. [PubMed: 20883478]

Veiga S, Melcangi RC, Doncarlos LL, Garcia-Segura LM, Azcoitia I. Sex hormones and brain aging. Exp Gerontol. 2004; 39:1623–31. [PubMed: 15582278]

Velíšek L, Velíšková J, Etgen AM, Stanton PK, Moshe SL. Region-specific modulation of limbic seizure susceptibility by ovarian steroids. Brain Res. 1999; 842:132–8. [PubMed: 10526103]

Velíšková, J. Behavioral characterization of seizures in rats. In: Pitkanen, A.; Schwartzkroin, PA.; Moshe, SL., editors. Models of seizures and epilepsy. Elsevier; San Diego: 2006a. p. 601-11.

Velíšková J. The role of estrogens in seizures and epilepsy: the bad guys or the good guys? Neuroscience. 2006b; 138:837–44. [PubMed: 16310960]

Velíšková J. Estrogens and epilepsy: why are we so excited? Neuroscientist. 2007; 13:77–88. [PubMed: 17229977]

Velíšková, J. Sex Differences in Seizure Sensitivity. In: Schwartzkroin, PA., editor. Encyclopedia of Basic Epilepsy Research. Academic Press; Oxford: 2009. p. 523-526.

Velíšková J, De Jesus G, Kaur R, Velíšek L. Females, their estrogens, and seizures. Epilepsia. 2010; 51(Suppl 3):141–4. [PubMed: 20618420]

Velíšková J, Moshe SL. Update on the role of substantia nigra pars reticulata in the regulation of seizures. Epilepsy Curr. 2006; 6:83–7. [PubMed: 16761069]

Velíšková J, Velíšek L. β-Estradiol Increases Dentate Gyrus Inhibition in Female Rats via Augmentation of Hilar Neuropeptide Y. J Neurosci. 2007; 27:6054–63. [PubMed: 17537977]

Velíšková J, Velíšek L, Galanopoulou AS, Sperber EF. Neuroprotective effects of estrogens on hippocampal cells in adult female rats after status epilepticus. Epilepsia. 2000; 41:S30–5.

Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. Nat Rev Neurol. 2011; 7:31–40. [PubMed: 21135885]

Vincent A, Crino PB. Systemic and neurologic autoimmune disorders associated with seizures or epilepsy. Epilepsia. 2011; 52(Suppl 3):12–7. [PubMed: 21542840]

Weiland NG. Glutamic acid decarboxylase messenger ribonucleic acid is regulated by estradiol and progesterone in the hippocampus. Endocrinology. 1992; 131:2697–702. [PubMed: 1446611]

Weintraub A, Singaravelu J, Bhatnagar S. Enduring and sex-specific effects of adolescent social isolation in rats on adult stress reactivity. Brain Res. 2010; 1343:83–92. [PubMed: 20438720]

Wheless JW, Kim HL. Adolescent seizures and epilepsy syndromes. Epilepsia. 2002; 43(Suppl 3):33–52. [PubMed: 12060005]

Wilkinson M, Bhanot R, Pincock JA, Donald L. Flurothyl-induced convulsions delay the onset of sexual maturation in the female rat. J Endocrinol. 1982; 95:37–41. [PubMed: 6813415]

Woolley CS. Effects of estrogen in the CNS. Curr Opin Neurobiol. 1999; 9:349–54. [PubMed: 10395567]

Woolley CS. Estradiol facilitates kainic acid-induced, but not flurothyl-induced, behavioral seizure activity in adult female rats. Epilepsia. 2000; 41:510–5. [PubMed: 10802755]

Woolley CS. Acute effects of estrogen on neuronal physiology. Annu Rev Pharmacol Toxicol. 2007; 47:657–80. [PubMed: 16918306]

Woolley CS, McEwen BS. Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat. J Comp Neurol. 1993; 336:293–306. [PubMed: 8245220]

Woolley CS, McEwen BS. Estradiol regulates hippocampal dendritic spine density via an N-methyl-D-aspartate receptor-dependent mechanism. J Neurosci. 1994; 14:7680–7687. [PubMed: 7996203]

Yague JG, Azcoitia I, DeFelipe J, Garcia-Segura LM, Munoz A. Aromatase expression in the normal and epileptic human hippocampus. Brain Res. 2010; 1315:41–52. [PubMed: 19815003]

Table 1

Epilepsy syndromes, which show sex differences in incidence

Some epilepsy/seizure syndromes more common in females	Some epilepsy/seizure syndromes more common in males
Idiopatic generalized epilepsy (Christensen et al., 2005) Aicardi syndrome (Ryan et al., 1997) Rett syndrome (Ryan et al., 1997)	Ohtahara syndrome (Clarke et al., 1987) Infantile spasms (Luthvigsson et al., 1994) Lennox-Gastaut syndrome (Trevathan et al., 1997) generalized myoclonic epilepsies (Nordli, 2005) Landau-Kleffner syndrome (Mouridsen, 1995) Febrile seizures (Forsgren et al., 1990; Tsuboi, 1984)

Table 2

Serum levels of ovarian hormones in healthy subjects

Physiological levels of estrogen and progesterone during the ovarian cycle in healthy women (Guerrero et al., 1976; Redei and Freeman, 1995)		
Serum Levels (pg/mL)	Follicular Phase	Luteal Phase
Estrone (E1)	60–200	60–100
Estradiol (E2)	50–350	100–200
Estriol (E3)		10
Progesterone	2,000–3,000	2,000–20,000
Physiological levels of estrogen and progesterone during the four-day ovarian cycle in rats (Scharfman et al., 2005; Smith et al., 1975)		
Serum Levels (pg/mL)	Estrus/Diestrus 1	Diestrus 2/Proestrus
Estradiol (E2)	7–20	30–40
Progesterone	1,000–5,000	5,000–20,000
Serum levels of estrogen and progesterone following different hormonal replacement regimens in ovariectomized rats		
Hormone dose administered		Serum levels (pg/mL)
Estradiol benzoate 2 μg/day (Neal-Perry et al., 2005)		27
β-Estradiol 0.1 mg/21 day capsule corresponds to 5 μg/day (Hoffman et al., 2003)		43
Estradiol benzoate 10 μg/day (Woolley and McEwen, 1993)		140
Estradiol benzoate 20 μg/day (Reibel et al., 2000)		141
β-Estradiol 0.5 mg/21 day capsule corresponds to 24 μg/day (Hoffman et al., 2003)		242
Progesterone 1–4 capsules (filled with crystalline P) (Hoffman et al., 2003)		11,000–28,000
Progesterone 6 capsules (filled with crystalline P) (Hoffman et al., 2003)		48,000

Table 3

Summarized effects of female sex hormones on kainic acid-induced seizures in ovariectomized rats

Interval OVX- KA (days)	HRT	HRT dose (μg/day)	Physiological range *	HRT duration prior to KA (days)	Effect on clonic seizure onset **	Seizure severity	Mortality	Neuroprotection	Reference
9	EB	2 μg/day	yes	2	anticonvulsant	No effect	decreased	yes	(Velíšková et al., 2000)
12	EB	2 μg/day	yes	4	anticonvulsant	No effect	NT	yes	(Velíšková and Velíšek, 2007)
40	EB	20 μg/day	no, ↑	5	No effect	No effect	NT	yes	(Reibel et al., 2000)
40	**EB**	**40 μg/day**	**no, ↑↑**	5	**proconvulsant**	NT	NT	**NT**	(Reibel et al., 2000)
14	β- E2	0.1 mg/21 day capsule * (corresponds to 5 μg/day)	yes	7	NT	No effect	decreased	yes	(Hoffman et al., 2003)
14	β- E2	0.5 mg/21 day capsule * (corresponds to 24 μg/day)	no, ↑	7	NT	No effect	decreased	yes	(Hoffman et al., 2003)
14	P	1–4 capsules *	yes	7	NT	decreased	decreased	Not applicable ***	(Hoffman et al., 2003)
14	**P**	* 6 capsules	**no, ↑**	7	NT	**No effect**	decreased	no	(Hoffman et al., 2003)

Table includes only studies using non-stressed rats and ovariectomized more than 7 days prior to seizure testing (see main text for explanation)

* See Table 2 for actual serum level measurements

** Onset of a first secondary generalized kainic acid-induced seizure (clonic seizure) is chosen because it provides a reliable measure of an anticonvulsant/proconvulsant effect. Onset of freezing and other abnormal behavioral or automatisms associated with focal limbic seizures (i.e., staring, chewing, wet-dog-shakes) is often subjected to a bias and as a reliable measure can be used only in conjunction with intrahippocampal EEG recordings (Velíšková, 2006a).

*** Decrease in seizure severity prevents evaluation of seizure-induced neuronal damage (i.e., no seizure=no damage)

Abbreviations: EB= 17β-estradiol 3-benzoate, slowly releasable form of β-estradiol (β-E2) with protracted effect to ensure stable serum levels of β-E2 following a single daily injection; P= progesterone; HRT = hormone replacement therapy; OVX = ovariectomy; KA= kainic acid; NT= not tested.;